REMARKS

Rejection of Claims and Traversal Thereof

In the December 17, 2003 Office Action,

claims 14-25, 27, 29, 38-61, 65 and 66 were rejected under 35 U.S.C. §112, second paragraph;

claims 14-25, 27, 29, 38-61, 65 and 66 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al. (WO 96/00583) and Johnson (U.S. Patent No. 5,658,785) in further view of over Whittle, et al. (U.S. Patent No. 5,955,087);

claims 16, 18, 20 and 50 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al. (WO 96/00583), Johnson (U.S. Patent No. 5,658,785) and Whittle, et al. (U.S. Patent No. 5,955,087) in further view of Gissmann, et al. (WO 96/11272); and

claim 61 stands rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al. (WO 96/00583), Johnson (U.S. Patent No. 5,658,785) and Whittle, et al. (U.S. Patent No. 5,955,087) in further view of Stanley, et al. (U.S. Patent No. 6,096,869).

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is requested in light of the following remarks.

Rejection under 35 U.S.C. §112, second paragraph

Claims 14-25, 27, 29, 38-61, 65 and 66 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to the Office,

> "upon review of the specification, there does not appear to be the specific teaching that E6 and E7 by themselves are transforming proteins. Moreover, a review of the entire disclosure does not indicate that these ORF were considered

> transforming, nor if they were considered such, any teaching on how to modify theses sequences to be 'non-transforming'."

The Office further states that:

> "neither E6 nor E7 are recognized to be transforming proteins."

Applicants vigorously disagree and submit that at the time applicants filed the present application, both E6 and E7 were considered to be genes that encode for proteins that are considered "transforming" by those skilled in the art.. Evidence of such known information can be found in Swan *et al.* (Arch Virol, 1994) provided to applicants in the January 2, 2003 Office Action. Specifically Swan, et al. expressly states at page 106 that:

> "E6 and E7 from the oncogenic HPVs bind to and inactivate several of the tumor suppressors [16, 20 64]. . . . The low risk HPVs have E6 and E7 proteins that bind tumor suppressor proteins with low affinity and transform much less efficiently [20, 35, 64]."

Further explanation for the transformation process can be found at page 106, first full paragraph, of the Swan review article, wherein it specifically states:

> "The high-risk HPVs can transform established cell-lines [67] and in the presence of an activated oncogene HPVs bind to and inactivate several of the tumor-suppressors [16, 20, 64]. Integration of high-risk HPVs probably affects transformation by increasing E6/E7 levels, thus decreasing the activity of the tumor suppressors. The low risk HPVs have E6 and E7 proteins that bind tumor suppressors proteins with low affinity and transform much less efficiently."

Thus, it is well known in the art that expressed E6 and E7 E6 proteins are considered transforming by participating in events that lead to transformation. For example, it is known that E6 protein binds to p53 thereby blocking the ability of p53 to bind DNA which leads to loss of control of cellular events. Likewise the E7/Rb1 binding results in deregulation of crucial cellular events.

Numerous articles reinforce the transforming properties of E6 and E7 proteins. For example, a primary source of molecular biology, The Encyclopedia of Molecular Biology, published in 1994, expressly states that E6 and E7 have transforming abilities. Specifically, at page 789, (a copy submitted on April 2, 2003) the proteins are discussed as follows:

> "**E6,E7.** The major proteins encoded by papillomaviruses that are relevant to transformation are transcribed from the E6 and E7 ORFs."

Further, a 1995 article by Tommasino, et al. (copy submitted on April 2, 2003) states that:

> "[E]xtensive studies on HPV E6 and E7 proteins have demonstrated their involvement in malignant transformation."

Thus, the E6 and E7 proteins encoded by the E6- and E7-ORF, respectively, are considered by those skilled in the art to be involved in transformation.

Additionally, applicants submit that it has been a well established axiom in patent law that a patentee is free to be his or her own lexicographer and thus may use terms in a manner contrary or inconsistent with one or more of their ordinary meanings, as long as the special definition of the term is clearly stated in the patent specification. *Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 38 USPQ2d 1126 (Fed. Cir. 1996). In other words, the specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication, and it is always necessary for the Examiner or the Court to review the specification in determining whether the inventor has used any terms in a manner inconsistent with their ordinary meaning. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979, 34 U.S.P.Q.2d 1321,1330 Cir. 1995) (en banc), aff'd, 116 S. Ct.1384, 38 U.S.P.Q.2d 1461,(1996).

So long as the meaning of an expression is made reasonably clear and its use is consistent within a patent disclosure, an inventor is permitted to define the terms of his claims. According to the Court in *Intellicall Inc. V. Phonometrics Inc.*, 21 USPQ2d 1383 (CAFC 1992), citing *Lear Siegler, Inc. v. Aeroquip Corp.*, 221 USPQ 1025, 1031 (Fed Cir. 1984) "the place to do so is in the specification of the inventor's application, and the time to do so is prior to that application acquiring its own independent life as a technical disclosure through its issuance as a United States patent." Therefore, the specification is **dispositive** as "**the single best guide to the meaning of a disputed term.**" *Vitronics Corp. v. Conceptronic Inc.*, 39 USPQ2d 1573, 1577 (Fed. Cir. 1996).

In *In re Barr,* 170 USPQ 330 (CCPA 1971), the Examiner rejected the claims that recite a photographic color coupler comprising a COUP radical that is "selected from the group consisting of a 5-pyrazolone coupler radical and an open-chain ketomethylene coupler radical"

and has substitution of a monothio radical in "**its coupling position**," for being indefinite under 35 U.S.C. 112, on the basis that most 5-pyrazolone radicals and open-chain ketomethylene radicals have "more than one coupling position" and that the applicants had failed to particularly point out in their claims at which of the plurality of possible coupling positions the monothio radical was substituted.

The Court, in reversing the Examiner's rejection of claims, stated that claims yet unpatented are given the broadest reasonable interpretation "**consistent with the specification**," and that the specification may serve "**as a dictionary for terms appearing in the claims**" and that the specification must be used in interpreting the claims and in determining their scope during the prosecution of a patent application, citing *In re Prater*, 415 F.2d 393, 162 USPQ 541 (CCPA 1969) and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (1970). Since the applicants had expressly stated in the specification that "[t]he 5-pyrazolene coupler radicals couple at the carbon atom in the 4-position, and the open-chain ketomethylene coupler radicals couple at the carbon atom forming the methylene moiety," which constitutes particularly precise definition of what the applicants meant by the phrase "its coupling position" recited in the rejected claims, the Court held that such claims are not indefinite, regardless of the Examiner's suggestion that most 5-pyrazolone radicals and open-chain ketomethylene radicals have "more than one coupling position" in the general sense of that phrase. See *In re Barr*, at 335.

Therefore, it is clear from the preceding case law that when a phrase **expressly recited in the claims** of a patent application has been **particularly defined by the specification**, the Office is bound to interpret such phrase consistent with the definition provided by the specification, even if such phrase may have multiple or alternative meanings in its ordinary usage.

In the present application, Applicants are requesting that the Office reads the claims in the light of the specification, by interpreting the claim limitation "non-transforming" in light of and in consistency with the definition of such term provided by the instant specification. Applicants have clearly defined the term "non-transforming" as any peptide or polypeptide, that is coded by an early papillomavirus gene (ORF) or fragment thereof, and is non-transforming by nature or intervention. Through intervention, the transforming ability of a polypeptide is destroyed by deleting a part of the ORF. A preferred non-transforming polypeptide is coded by a fragment of

the E6-E7 ORFs of a papillomavirus." Further, applicants define the term "transformation" as the "conversion of a normal cell into a tumor cell which has the capacity for unlimited proliferation."

Thus, one skilled in the art, reading the definition set forth in the application, would understand that "non-transforming" means that the polypeptide is no longer able to participate in the conversion of a normal cell line into a tumor cell having the capacity of unlimited proliferation. Since such phrase "a non-transforming polypeptide" is expressly recited by the claims of the present application, the definition provided by the instant specification for such terms is "dispositive" and constitutes "the single best guide to the meaning" of such phrase, according to *Vitronics Corp. v. Conceptronic Inc.*, 39 USPQ2d 1573, 1577 (Fed. Cir. 1996).

Clearly, the present disclosure is sufficient for one skilled in the art to practice the claimed invention, and as such, applicants request that all rejections under 35 U.S.C. §112, second paragraph be withdrawn.

Rejection under 35 U.S.C. §103 (a)

In the December 17, 2003 Office Action, claims 14-25, 27, 29, 38-61, 65 and 66 were rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al. and Johnson, and in further view of Whittle, et al. Applicants submit that Donnelly, et al. in combination with Johnson and Whittle, et al. does not render applicants' claimed invention *prima facie* obvious.

The present invention relates to an adeno-associated virus vector comprising a nucleotide sequence encoding a fusion polypeptide. The fusion polypeptide comprises a structural papillomavirus polypeptide and an E6 and/or E7 early papillomavirus polypeptide having the C-terminus of the structural papillomavirus polypeptide connected to the N-terminus of the E6 or E7 early papillomavirus polypeptide. Importantly, as defined in the application, the early papillomavirus peptide had been rendered non-transforming by deleting a section of the ORF that codes for a site that interacts with other proteins involved in the transformation cascade. As stated above, the specification, expressly states that "through intervention, the transforming ability of a (poly)peptide is destroyed by deleting a part of the ORF." It is further stated at page 4 of the present application that "[p]art of the E6-ORF has been deleted beforehand, so that the transforming properties of E6 were destroyed." Thus, applicants' vectors encode for a

transformation-deficient early papillomavirus polypeptide that reduces the risk of de novo tumor induction, yet can till trigger the immune system to mount an immune response against expressed antigens.

The Office has combined the teachings of Donnelly, et al., Johnson and Whittle, et al., in an attempt to establish a *prima facie* case of obviousness. However, applicants insist that such a combination does not in any teach or suggest applicants' claimed invention.

Initially, it should be noted that Donnelly, et al. teaches the use of DNA plasmids encoding for polypeptides of papillomavirus. Further, Donnelly teaches away from the use of any type of viral vectors. Specifically, Donnelly states, at page 4 of the specification, that:

> "Retroviral vectors have restrictions on the size and structure of polypeptides that can be expressed as fusion proteins while maintaining the ability of the recombinant virus to replicate, and the effectiveness of vectors such as vaccine for subsequent immunization may be compromised by immune responses against the vectors themselves. Also viral vectors and modified pathogens have inherent risks that may hinder their use in human."

Thus it is very evident that the use of any type **of viral vectors is disparaged by the Donnelly, et al. reference**.

According to the Office, AAV is not considered a retrovirus. Applicants agree but it should be noted that it is well known that both AAV and a retrovirus have similar abilities. Specifically, both retroviruses and adeno-associated viruses are known to have the ability to integrate their genetic material into that of the host cell. Clearly this is one of the reasons that Donnelly wants to avoid the use of viral vectors. Further, there are restrictions on the size of polypeptides that can be expressed in the AAV vector and clearly a concern includes an immune response against the virus because it is well known that the majority of us, as humans, have antibodies in our serum reactive against different AAV virus strains.

Furthermore, Donnelly, et al. states at the bottom of page 5 to the top of page 6 of the cited reference that:

> "The protective efficacy of DNA vaccination against subsequent viral challenge is demonstrated by immunization with non-replicating plasmid

> DNA encoding one or more of the above mentioned viral proteins. **This is advantageous since no infectious agent is involved, no assembly of virus particles is required, and determinant selection is permitted.**" (emphasis added)

It is evident that Donnelly, et al., used a non-replicating plasmid to avoid viral vectors and the use of an infectious agent.

The Office has combined the teaching of Johnson, et al. with Donnelly, wherein Johnson, et al. describes the use of AAV vectors for delivery of genetic material. However, in order to determine obviousness, it is incumbent upon the Office to consider the inventions of the cited references in their entireties. Certain individual features from the references may not be chosen and merely lumped together as a mosaic in an attempt to meet the features of the rejected claims. *In re Wesslau*, 174 U.S.P.Q. 393 (CCPA 1965). This legal concept is important for the Office to remember when attempting to combine prior art that teach entirely different methods of delivery of genetic material.

Applicants assert that if the teachings of Donnelly, et al and Johnson are combined then each individual delivery system will be rendered unsatisfactory for its intended use or change the principle of operation. According to the court in *In re Gordon,* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), if proposed modification would change the principal of operation of the prior art, then there is no suggestion or motivation to make the proposed modification.

Clearly if the teachings of Donnelly, et al. and Johnson are combined then both delivery systems would no longer operate as intended. For example, if the AAV vector of Johnson is used in the Donnelly, et al system to replace the non-infectious plasmid then the delivery system of Donnelly, et al. would include an infectious agent that could integrate into the genomic material of the infected cell. This possible occurrence is exactly what Donnelly, et al. is avoiding by use of a recombinant plasmid.

In the reverse, Johnson teaches the use of a viral vector and it is imperative that the ITR vector be included. There is no teaching or suggestion in Johnson that would indicate to one skilled in the art that the recombinant plasmid of Donnelly, et al. (lacking any genes of AAV) could replace the AAV vector in the Johnson system.

The Office states that Whittle was cited to provide "the specific teaching that at the time of filing HPV fusion proteins were used as vaccines and could be expressed by a vector." However, as stated above, the Office is not allowed to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. *In re Hedges*, 228 USPQ 685 (Fed. Cir. 1986). Whittle, et al. teaches fused polypeptides of HPV but the expression of the fused polypeptides is clearly set forth as a technique which can enhance and achieve high level of expression in heterologous cells, in particular *E. coli* bacterial cells. Whittle, et al. preferably uses the T7 expression system of *E coli* wherein recombinant polypeptides are found in insoluble aggregates within the cell. Moreover, the Whittle, et al. reference specifically discloses a method of preparing a suitable vector for expression of the polypeptide in *E. coli* bacteria cells by inserting a nucleic acid sequence which encodes the desired polypeptide but which has been mutated such that codons or groups of codons which cause premature termination of transcription or translation have been replace by degenerate codons. The reference discloses that by using the **T7 expression system**, the incidence of premature termination of transcription can effectively be prevented or reduced by removal of at least one poly-T sequence such as [TTT]n, by replacing such a sequence with an acceptable alternative, e.g. a [TTC]n sequence which encodes the same amino acids, leading to a higher yield of desired polypeptide. All the examples in the Whittle, et al. reference demonstrate the use of the T7 expression system.

As stated above, it is incumbent on the Office to provide some suggestion or teaching in the cited reference that would lead one skilled in the art to proceed in the direction of applicants' claimed invention. What is the asserted motivation in Whittle, et al. or Donnelly, et al. to use an adeno-associated virus vector of Johnson with a HPV fused polypeptide? The Courts have addressed this issue numerous times and have stated that "[t]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). Thus, this allegedly "obvious" direction is supported only by the Office's reinterpretation of the art in light of applicants' disclosure.

Further, even if the references were combinable, which they are not, the proposed combination does not teach each and every limitation of the presently claimed invention. Specifically, the

proposed combination does not in any way disclose, teach or suggest each and every element of the presently claimed invention because none of the cited references either alone or in combination teach or suggest a **fused polypeptide** comprising a structural papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of L1-ORF, L2-ORF and fragments thereof, and an early E6-ORF, E7-ORF or fragments thereof, **wherein a part of the early papillomavirus gene has been deleted thereby rendering the early papillomavirus polypeptide non-transforming.** By deleting a section of the E6-ORF or E7-ORF that encodes for the transforming properties, the expressed protein cannot bind to and inactivate tumor-suppressors, and thus, is rendered non-transforming.

Further, none of the cited references provides any motivation to go in the direction of applicants' claimed invention. As stated above, Donnelly, et al. teaches the use of one gene per plasmid. Whittle, et al. does not in any way, disclose, teach or suggest deleting any part of the E6-ORF or E7-ORF gene before inclusion in the prokaryotic expression system. The full E6-ORF or E7-ORF gene is included and the reference is devoid of any discussion relating to a deletion of a part of the genes to render any expressed proteins as non-transforming. Johnson is only related to **viral** vectors and does not address E7 and E6 proteins or encoding genes.

Further, the Office has failed to give any probative weight to the advantages and benefits of the present invention as part of the "invention as a whole" and instead has cited references that do **not in any way** disclose or teach such advantages. None of the references recognize that by inactivating the transformation abilities of E6 or E7 proteins there is a reduced likelihood of tumor formation, however, the transformation deficient protein will still trigger an immune response.

Thus, in light of the above discussion and the fact that each and every recited limitation of applicants' claimed invention is not disclosed or suggested in the cited references; there is no suggestion or teaching to combine said references; and if the Donnelly, et al and Johnson reference were combined, the mode of operation for each system would be changed; the cited combination fails to establish a *prima facie* case of obviousness of applicants' claimed invention.

Claims 16, 18, 20 and 50 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al., Johnson and Whittle, et al., in further view of Gissmann, et al. The Office must

view Gissmann, et al. in its entirety and if properly viewed, the cited reference in combination with the primary and secondary references still does not teach or suggest all the claimed limitations of the present invention. Gissmann, et al. discloses fused polypeptides wherein a portion of a viral structural proteins of HPV, whether L1 or L2, is deleted. In the deleted area of the sequence another sequence is inserted. This is in sharp contrast to Donnelly, et al. that expressly states that maintaining the conserved portions of the papillomaviruses, such as structural portions L1 and L2, is important to provide protection against subsequent challenges by different types of papillomaviruses. Donnelly, et al. maintains the integrity of the structural proteins for the specific reason of providing extended protection, even if a subsequent attack occurs by another virus strain. Clearly, mutating the L1 or L2 structural gene is precluded by Donnelly, et al. and as such the Gissmann, et al and Donnelly, et al. references are not combinable. More important, if the mutation of L1 and L2 as taught by Gissmann, et al. is introduced into the DNA constructs of Donnelly, et al. the intended purpose of maintaining a highly conserved structural protein in the Donnelly, et al. reference is destroyed. Thus, there is no motivation to combine the cited references and the Office has not provided any teachings or suggestions sufficient to provide one skill in the art the motivation to make the proposed modifications needed to arrive at applicants' claimed invention.

Further the addition of Gissmann to the previous proposed combination still does not teach all elements of applicants' claimed invention. Specifically, the combination does not teach or suggest a **fused polypeptide** comprising a structural papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of L1-ORF, L2-ORF and fragments thereof, and an early E6-ORF, E7-ORF, **wherein a part of the early papillomavirus gene has been deleted thereby rendering the early papillomavirus polypeptide non-transforming**.

In light of the above discussion and it is clear that the cited combination fails to establish a *prima facie* case of obviousness of applicants' claims as herein amended.

Claim 61 was rejected under 35 U.S.C. §103 (a) as being unpatentable over Donnelly, et al., Johnson and Whittle, et al. in further view of Stanley, et al. Regardless of the teachings of Stanley, et al. applicants respectfully submit that the defects in the alleged *prima facie* case over Donnelly, et al., Johnson and Whittle, et al. are not cured by the addition of Stanley, et al. Thus, for the reasons set forth above, this rejection also is improper.

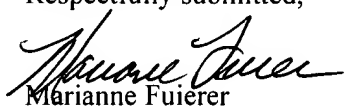
Stanley, et al. describes therapeutic compositions that include cytokine interleukin-12 and that are used not only as a immunotherapeutic for HPV tumors but also as an adjuvant in compositions that can further comprise early papillomavirus or structural polypeptides of HPV. However, as stated above, the addition of Stanley, et al. to the proposed combination still does not teach all elements of applicants' claimed invention. Specifically, the combination does not teach or suggest a **fused polypeptide** comprising a structural papillomavirus polypeptide encoded by an open reading frame selected from the group consisting of L1-ORF, L2-ORF and fragments thereof, and an early E6-ORF, E7-ORF, **wherein a part of the early papillomavirus gene has been deleted thereby rendering the early papillomavirus polypeptide non-transforming**

In light of the reasons set forth above and the clarifying amendments to the claims, applicants submit that the cited references fail to suggest the subject matter of the currently amended claims. Reconsideration and withdrawal of the rejections under 35 U.S.C. §103 (a) is respectfully requested.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Woitach reconsider the patentability of pending claims in light of the distinguishing remarks herein and withdraw all rejections; thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Woitach is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,



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